PATENT
Customer No. 22,852
Attorney Docket No. 09526.0001-01000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	
Jacques FASTREZ et al.	Group Art Unit: 1652
Application No.: 08/978,607	Examiner: Tekchand Saidha
Filed: November 26, 1997	
For: CHIMERIC TARGET MOLECULES HAVING A REGULATABLE ACTIVITY	Confirmation No.: 4607

Mail Stop Appeal Brief—Patents
Commissioner for Patents
P.O. Box 1450
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Sir:

REPLY BRIEF UNDER 37 C.F.R. § 41.41

Pursuant to 37 C.F.R. § 41.41, Appellants present this Reply to the Examiner's Answer dated June 29, 2005. A Request for Oral Hearing is concurrently filed with this Reply Brief. If any additional fees are required or if the enclosed payment is insufficient, please charge the required fees to Deposit Account No. 06-0916.

I. Introduction

Claims 13-35, 37, and 38 are pending in this application. Claims 1-12 and 36 have been canceled. In the Examiner's Answer dated June 29, 2005, the Examiner withdraws the rejection of claims 13 and 20 under 35 U.S.C. § 102(a) and (b), as well as the rejection of claim 24 under 35 U.S.C. § 112. *See* Examiner's Answer mailed June 29, 2005 ("Answer"), at 3 and 19 (items 6 and 13, respectively). The Examiner

maintains that claims 13-23 and 25-29 fail to comply with the enablement and written description requirements of 35 U.S.C. § 112, first paragraph. Thus, claims 30-35, 37, and 38 are allowed, claim 24 is objected to, and claims 13-23 and 25-29 are rejected. Claim 24 depends from a rejected claim and would be allowable if re-written in independent form.

The Examiner and Appellants appear to agree that the claims on appeal are directed to methods for determining the presence or amount of an analyte in a test sample comprising detecting the amount of catalysis of a substrate by a chimeric enzyme comprising a starting enzyme and a mimotope. *See* Answer at 21 ("it must be clarified that at the beginning of the enablement and written description rejections – it was clearly stated that the claims are "method claims" and nothing but "method claims"). However, the Examiner and Appellants part company on what the specification must enable and describe in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph, for the claimed methods.

Appellants contend that the specification must enable one skilled in the art to perform the steps of the claimed methods for the range of analytes encompassed by the claims. The Examiner does not appear to dispute Appellants' position that the specification describes sufficient chimeric enzymes comprising a β-lactamase starting enzyme to meet this standard. *See, e.g.*, Answer at 3. According to the Examiner, however, the specification must enable one skilled in the art to make chimeric enzymes from "any enzyme from any source," Answer at 6, despite the uncontested fact that the rejected claims do not recite any step for preparing a chimeric enzyme, and despite the

absence of a reasoned argument or evidence from the Examiner to support his notion that chimeric enzymes beyond those described and enabled by the specification are necessary to the practice of the invention.

Appellants further contend that, in order to satisfy the written description requirement, the specification must describe a sufficient number of chimeric enzymes to demonstrate that, at the time the application was filed, they were in possession of assays for the range of analytes encompassed by the claims. Again, the Examiner does not appear to dispute Appellants' position that the specification describes sufficient chimeric enzymes comprising a β-lactamase starting enzyme to meet this standard. *See, e.g.*, Answer at 17-18. According to the Examiner, however, the specification must describe a representative number of chimeric enzymes from "the claimed genus from any organism." *Id.* at 17.

Appellants respectfully continue to disagree with the maintained rejections for the reasons of record as supplemented below.

II. The Full Scope of the Claims is Enabled

As noted above, the Examiner acknowledges that assay methods using a chimeric enzyme comprising a β-lactamase starting enzyme are enabled (*see, e.g.*, claim 24 and Answer at 3), but that methods using other starting enzymes are not adequately enabled. The Examiner's rationale is apparently that the specification does not describe how to make and use chimeric enzymes comprising non-β-lactamase starting enzymes without undue experimentation.

The claimed methods, however, are based on detecting changes in enzymatic activity on binding of a binding molecule to a mimotope. The novel and non-obvious methods use chimeric enzymes merely as a detectable label. There simply is no need to change the identity of the detectable label in order to practice the full scope of the claimed assays. Because the chimeric enzymes are not claimed,[1] the patentability of those enzymes over the prior art is irrelevant—the Examiner's contentions to the contrary are specious. *See* Answer at 14 ("Such a definition [of the nature and extent of changes to enzymes] might also read on previously characterized proteins. . ."). Like other novel detection assays, the novelty of the manipulative steps of the methods and the readily apparent interchangeability of the label used (here, a chimeric enzyme) entitles the Appellants to the breadth of the methods that the specification provides based on the procedures that they developed.

To satisfy the enablement requirement, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. *Atlas Powder Co. v. E.I. Du Pont de Nemours*, 750 F.3d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984) ("That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive.") The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, and must "explain why [he] doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions

[1] Despite apparent agreement that chimeric enzymes are not claimed in this application, *see, e.g.*, Answer at 5, the Examiner persists in mistakenly referring to the chimeric enzymes used in the methods as "the claimed genus" or the "enzyme construct such as those claimed." Answer at 17 and 24, respectively.

of [his] own with acceptable evidence or reasoning." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). It is only the claimed invention for which enablement is required, not unclaimed features of the same. *See, e.g.*, *Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F. Supp. 1278, 1292, 6 USPQ2d 1065, 1073 (D. Del. 1987) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983) and *DeGeorge v. Bernier*, 768 F.2d 1318, 1323, 226 USPQ 758, 763 (Fed. Cir. 1985)).[2]

As described below, in rejecting the claims directed to using non-β-lactamase chimeric enzymes under 35 U.S.C. § 112, the Examiner misstates the scope of the claims and the content of the supporting disclosure. As a consequence, he fails to provide sufficient basis to question the objective evidence of enablement set forth in the specification to meet his burden to establish a *prima facie* case of non-enablement. Even if the burden shifts to the Appellants to show that the disclosure directs a skilled artisan how to make the genus of chimeric enzymes recited in the claimed methods without undue experimentation (as the Examiner contends), Appellants provide argument and objective evidence that outweighs the Examiner's conclusory statements

[2] The Examiner questions the relevance of *Phillips Petroleum* because Appellants did not explain how the facts in that case are analogous to the facts here. Answer at 10. As should be obvious from Appellants' Opening Brief, however, *Phillips Petroleum* was cited to support Appellants' statement that the law requires only that the specification enable that which is claimed. Appeal Brief Under Board Rule § 41.37 ("Opening Brief") at 11. An analysis of the facts of *Phillips Petroleum* is not required to understand this well established principle of the law. In *Phillips Petroleum*, the court held that an enabling disclosure of an unclaimed limitation is not relevant to enablement of the claimed invention. 673 F. Supp. at 1292, 6 USPQ2d at 1074. Here, Appellants are not claiming chimeric enzymes, but only methods of using those enzymes.

about the unpredictability of the art and undue experimentation in the same. *See, e.g., In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

A. The Examiner Errs by Rejecting Claims Based on Alleged Non-Enablement of a Limitation That Is Not Claimed

As a threshold matter, the pending claims are directed to methods that comprise mixing a chimeric enzyme with a test sample and a substrate, and detecting the amount of catalysis of the substrate by the chimeric enzyme. The chimeric enzyme of the methods comprises a starting enzyme and a mimotope, and includes the functional limitation that the activity of the chimeric enzyme is modulated upon binding of a binding molecule to the mimotope. The claims also define how the mimotope is positioned in relation to the starting enzyme: it is "inserted in said enzyme or replacing at least one amino acid of said enzyme."

The Examiner incorrectly characterizes the claims, to import a limitation that is not recited therein. For example, he alleges that "[t]he claims are directed to a method for determining the presence of an analyte in a test sample using any enzyme as the starting enzyme, modifying the enzyme(s) to create a functional or enzymatically active chimeric enzyme having a binding site moiety, to which a binding molecule can attach." Answer at 6 (emphasis added). Similarly, when characterizing the claimed method, the Examiner lists only a single step – one that is nowhere recited by the claims. Answer at 5 ("The claims are directed to a method of determining the presence of an analyte using any (a) chimeric enzyme as the starting enzyme, wherein said chimeric enzyme is constructed by inserting a sequence of said mimotope (binding site moiety) into a sequence of said starting enzyme by replacing at least one amino acid of the stating

enzyme with a sequence of said mimotope") (emphasis original). Portions of the Answer confuse chimeric enzymes and starting enzymes,[3] and others require constructing a chimeric enzyme by "first produc[ing] a chimeric enzyme and further attempt[ing] to selectively insert mimotopes." *See, e.g.*, Answer at 6-7.

The Examiner then rejects the claims for allegedly failing to enable the imported claim limitation. The Examiner thus states that the claims require "modifying" or "constructing" an enzyme to form a chimeric enzyme, and misapplies the enablement standard to allege that the claimed methods are not enabled because particular methods to make a chimeric enzyme from *any* starting enzyme are not sufficiently described. *See, e.g.*, Answer at 7 ("[The specification] lacks adequate guidance because the chimeric insertion developed for β-lactamase by insertion of specific mimotopes to achieve binding in β-lactamase may not necessarily function with any enzyme"); *see also*, Answer at 12. In other words, the Examiner requires that the specification enable methods of making non-β-lactamase chimeric enzymes by "modification of mimotope amino acid(s) and its insertion into any enzyme,"[4] whereas to enable the methods using chimeric enzymes, enablement of the steps of the method is required. Enablement of any method to make the chimeric enzymes that are used in the claims will suffice, if such enablement is required. *See, e.g.*, *Ex parte Erlich*, 3 USPQ2d 1011, 1013 (Bd. Pat. App. & Int. 1986) (holding that claims are enabled

[3] For example, at page 4 of the Answer, the Examiner states that the methods use "a chimeric β-lactamase as the starting enzyme," and as noted above, at page 5 the Examiner states that the methods "us[e] any [] chimeric enzyme as the starting enzyme." To be clear, chimeric enzymes are produced from the starting enzyme.
[4] Answer at 7.

regardless of whether a preliminary screening assay was disclosed in sufficient detail because "the claims on appeal do not require the use of the assay in dispute.") Appellants respectfully submit that if the Examiner is correct that the full scope of chimeric enzymes that might possibly be useful in the claimed methods must be separately enabled for a skilled artisan to practice the methods, then no method to using chimeric enzymes comprising a starting enzyme and a mimotope would satisfy the enablement requirement.[5]

By repeating that the claims require a specific method of modifying the starting enzyme, the enablement enquiry is diverted from the enablement of the steps of the claimed methods (addressed in the Appellants' Opening Brief), and toward enablement of a modification/construction step that is not claimed. Because the method of making a chimeric enzyme is not recited in the claims, the Examiner errs in requiring particular methods of making any chimeric enzyme and errs in requiring that Appellants establish that the method must "necessarily function."

B. The Examiner Errs in Contending that the Specification Enables Only a β-Lactamase Starting Enzyme

Although the Examiner maintains that the specification only provides guidance for a β-lactamase starting enzyme, see Answer at 5, lines 10-14 and at 16, lines 11-15,

[5] The Examiner urges that Appellants misinterpret a portion of the Advisory Action to suit this appeal, effectively misquoting the Action by omitting a portion of a sentence at page 4. (*See* Answer at 12, referring to Opening Brief at 12.) The Appellants, however, wish to clarify that at pages 12-14 of the Opening Brief, Appellants argue the enablement of the *claimed steps* of the methods. In contrast, the Examiner maintains that an *unclaimed step* ("chimeric insertion developed for β-lactamase") allegedly fails to "necessarily function with any enzyme," when the proper test is whether a skilled artisan, reading the specification, could practice the claimed assay methods without undue experimentation. *See, e.g., W. L. Gore*, 721 F.2d at 1557, 220 USPQ at 316.

many other enzymes and their properties are set forth in the specification as filed. The relevance of this guidance was argued, for example, in the Opening Brief at 17, line 11 to 18, line 16, to which argument the Examiner did not respond in his Answer. It is well established that "[t]he first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Accordingly, the Examiner's repeated assertions that the specification provides only "a single site specific chimeric β-lactamase" are in error, *see, e.g.*, Answer at 5, line 11, and at 18, lines 3 and 17, because the Examiner fails to address Appellants' arguments regarding enablement. *Marzocchi*, 439 F.2d 220, 223, 169 USPQ at 369 ("[A] specification disclosure . . . *must* be taken as in compliance with the enabling requirement of the first paragraph of 112 *unless* there is reason to doubt the objective truth of the statements contained therein") (emphasis original).

In rebuttal to Appellants' enablement argument, the Examiner does not appear to acknowledge the disclosure of and guidance relating to making non-β-lactamase chimeric enzymes in the specification, instead asserting that "it is clear that all the guidance, exemplification, etc., provided in the specification relate to an assay method utilizing β-lactamase chimeras with mimotopes inserted at specific insertion sites of the β-lactamase enzyme from E. coli." Answer at 16.

The specification as-filed provides substantial guidance relating to starting enzymes, generally, and chimeric enzymes comprising the full scope of chimeras as well. In certain embodiments, enzymes and their specific sites for positioning a

mimotope are specifically described. In one instance, the specification directs the skilled artisan to modulate chymotrypsinogen by inserting a mimotope to modulate proteolytic cleavage of the peptide bond Arg 15-Ile 16, and analogous peptide cleavage mechanisms to activate other zymogens into enzymes, such as other serine proteases, are also set forth. Specification at 9. Similarly, modulation of the phosphorylation of glycogen phosphorylase on Ser 14 by the binding of a binding molecule to an engineered mimotope is specifically described, as are enzymes for which phosphorylation regulates enzyme activity. *Id.*

Starting enzymes with well known and well characterized selectable activities are also provided in the specification, including enzymes that are available in phage display constructs (and references for obtaining the same) for ease of chimeric enzyme selection using precisely the same approaches exemplified for β-lactamase, e.g., plasmin, prostate specific antigen, subtilisin, trypsin, alkaline phosphatase, β-galactosidase, Staphylococcal nuclease, glutathione transferase, lysosyme, and catalytic antibodies. Specification at 5- 6. Further, the specification provides additional exemplary starting enzymes for methods to detect an analyte with a chimeric enzyme, such as, e.g., esterases, pyruvate kinase, glucose oxidase, lactate dehydrogenase, glucose-6-phosphate dehydrogenase, and luciferase. Specification at 6.

The specification states that starting enzymes are selected for a desired selectable activity for use as labels in the methods of the invention. The enzymatic activities, primary, secondary, and in some cases tertiary structural information for these exemplary starting enzymes were well known to a skilled artisan at the time this

application was filed. Like β-lactamase, these exemplary enzyme species have been displayed on phage and are directly amenable to selection for a desired activity.

The Examiner fails to consider this guidance when maintaining the enablement rejection, instead insisting that working examples that provide 50 million chimeric β-lactamase enzymes are not relevant and not enabling for chimeric enzymes more broadly. Although the Examiner alleges that the skilled artisan would need the primary sequence for the starting enzymes (as well as insertion sites, catalytic or binding sites, etc.), Answer at 8, lines 7-15, such information was well known and readily apparent to a skilled artisan (and often also set forth in references cited in the specification) when the application was filed. It is well established that the specification does not have to disclose that which is well known or readily apparent to one of ordinary skill in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) ("[A] patent need not teach, and preferably omits, what is well known in the art.") As such, a patent specification does not have to provide an enabling disclosure of starting materials that are readily known or available to one of skill in the art. *In re Brebner*, 4455 F.2d 1402, 1404, 173 USPQ 169, 171 (CCPA 1972). Further, patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. *Ex parte Obukowicz*, 27 USPQ2d 1063, 1069 (Bd. Pat. App. & Int. 1992).

Thus the Examiner errs in his characterization of the facts, he fails to address the full scope of the guidance provided in the specification as filed, and his analysis of the *In re Wands* balancing test for undue experimentation is flawed. As described below,

even if the Examiner is correct that the specification must enable the skilled artisan to make chimeric enzymes from any starting enzyme, the Examiner's analysis of the undue experimentation factors is flawed by his failure to address the general enabling disclosure in addition to the working examples. Appellants present evidence herein that establishes enablement of the full scope of the claims.

C. One Skilled in the Art Would Apply the Guidance of the Specification to Make a Chimeric Enzyme Without Undue Experimentation

Appellants submit that the Examiner has not established a *prima facie* case of non-enablement. Even if the evidence relied on by the Examiner was enough to shift the burden to Appellants, a full examination of the evidence relevant under *In re Wands* establishes that the full scope of the claims is enabled. In his Answer, the Examiner asserts that Appellants have "clearly misinterpreted the *Wands* factors in relation to what is enabled by the instant specification," Answer at 16, and that Appellants "have failed to address the key issues of the rejection," Answer at 13. On these contentions, the Examiner is flatly wrong.

Appellants devote five pages of the Opening Brief to an analysis of the factors set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), arguing enablement of chimeric enzymes generally, based on the working examples, the guidance provided in the specification, and objective evidence of the level of skill and predictability in the art. *See* Opening Brief at 14-18. The Examiner never addresses these arguments, instead he asserts that it is not necessary to address every *Wands*

factor, citing MPEP § 2164.01(a), and choosing to ignore the factors that do not favor his outcome.[6]

Like the Court's analysis of the facts in *In re Wands*, an analysis of the facts of this case establishes that the application provides sufficient guidance and examples to allow a skilled artisan to make and use the claimed methods without undue experimentation. While enablement of each case is analyzed on its facts, the facts of *Wands* are remarkably similar to the fact of this case. To the extent that the facts of this application differ, the differences tend to favor enablement. For example, the level of skill in the art when the instant application was filed in 1997 is much higher than it was 15 years earlier when the Wands et al. application was filed.

For the Wands et al. patent, U.S. Patent No. 4,879,219, the Court concluded that methods for using high affinity IgM antibodies were enabled when "the disclosure provides considerable direction and guidance . . . [t]here was a high level of skill in the art at the time the application was filed, and all of the methods needed to practice the invention were well known." *In re Wands*, 858 F.2d at 740, 8 USPQ2d at 1406.

Similarly, the Federal Circuit upheld the enablement of claims directed to methods for preparing any bacterial strains which produce any amino acids using any amplifying vector (U.S. Patent No. 4,278,765), based on the description of supplementation of a single amino acid using a single vector in one recipient strain to

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[6] MPEP § 2164.01(a) does not support the proposition for which it is cited by the Examiner, instead stating in part "It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more others. The Examiner's analysis must consider all the evidence related to each of these factors."

make two recombinant bacterial strains. *See Ajinomoto Co. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345, 56 USPQ 1332, 1337 (Although "the claims could cover myriad bacterial strains not yet known . . . practitioners of this art were prepared to carry out the identification, isolation, recombination, and transformation steps required to practice the full scope of the claims.") The Court also found no error in the district court's determination that "the patent was enabled since the types of mutations suggested by the patent were conventional and one skilled in the art could easily produce such mutants because genetic engineering techniques were conventional and well-known." *Id.* As the patent in *Ajinomoto* was filed in 1979, techniques well-known in 1979 must necessarily be well-known in 1997 at the priority date for this application.

And finally, a patent that broadly claims sandwich immunoassays but provides examples of antibodies to a single antigen (U.S. Patent No. 4,376,110), has been challenged on enablement grounds and upheld at the Federal Circuit. *See, e.g.*, Hybritech, 802 F.2d at 1384, 231 USPQ at 94 (holding that because the monoclonal antibodies can be obtained by a well-known process, and the screening methods used to identify the necessary characteristics were well-known in the art, "there was not a shred of evidence that undue experimentation was required.")

This application merely relies on genetic engineering and molecular biology techniques that were well-known to the skilled artisan at the time of filing. In this application, Appellants provide many exemplary starting enzymes, many mimotopes, and disclose how to use well-known techniques for combining the same to make a chimeric enzyme. Methods to create libraries of chimeric enzymes and to screen for

chimeric enzymes with desired properties were successfully applied five times to β-lactamase. Thus, like in *Wands*, the application provides considerable direction and guidance, the level of skill in the art would be at least as high as the level applied to the Wands analysis, and the methods needed to practice the invention are provided in the specification and/or well-known.

Nevertheless, the Examiner asserts without citing specific authority, that modification of a variety of starting enzymes to create an active chimeric enzyme is unpredictable because modification will not necessarily result in producing an active chimeric enzyme. *See, e.g.*, Answer at 7. This is not the test for enablement. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976) (emphasis added); *accord*, *Atlas Powder*, 750 F.2d at 1576-77, 224 USPQ at 413. To establish a *prima facie* case of non-enablement, the Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. *Id.* In the present case, the Examiner has not met this burden. Although the Examiner may have demonstrated that some experimentation is necessary, doing so is not enough to shift the burden to Appellants to prove that such experimentation is not undue. *Angstadt*, 190 USPQ at 219.

The specification guides the skilled artisan to select a starting enzyme with well-known activity, to identify and select positions for incorporation of a mimotope sequence, as well as to perform efficient screens for enzymes that modulate their activity on binding to a binding molecule. *See, e.g.*, Opening Brief at 16-18, and *supra*.

The specification further directs the skilled artisan to select a starting enzyme with a desired detectable activity, and discloses exemplary starting enzymes having the same. *See*, Specification at 5-9.

The guidance on selection of a site for mimotope addition to a starting enzyme at 11, lines 5 to 12, line 4 of the specification sets out three factors for selecting a modification site. *See*, Opening Brief at 17-20. One skilled in the art, reading the specification, would readily apply the guidelines of the specification at page 11 with the well known characteristics of the selected starting enzyme, to identify a small number of potential positions for modification with a mimotope such that the starting activity of the resulting chimeric enzyme is maintained. *See In re Barrett*, 169 USPQ 560 (CCPA 1971) (claims are enabled "[if] selection of an appropriate membrane would [] have been within the ordinary skill in the art"); *see also, Atlas Powder*, 750 F.3d at 1576, 224 USPQ at 414 (holding that claims are enabled when a skilled artisan would apply well known principles to select combinations that would work from a general disclosure). Assays to detect whether the chimeric enzymes retain activity of the starting enzyme and to detect whether the binding of a binding molecule to the mimotope modulates the enzymatic activity are well known and/or set forth in the specification as filed. *See*, *e.g.*, Specification at 10, line 18, to 11, line 4.

Further, it would be readily apparent to a skilled artisan that the starting enzyme and mimotope can be combined by many well known techniques to create specific substitutions or insertions in the starting enzyme sequence or to create the libraries of modifications described, for example, in Example 1. The five libraries containing 50

million chimeric β-lactamase enzymes indicate to the skilled artisan that given the selection assays and screens known in the art and set forth in the specification, modification of a non-β-lactamase starting enzyme, for example to produce a heterogenous library of chimeric enzymes, could be carried out to identify chimeric enzymes, wherein the activity of the chimeric enzyme is modulated upon binding of a binding molecule to the mimotope. The application discloses a variety of techniques for constructing a chimeric enzyme, e.g., cloning, site-directed mutagenesis, homologous recombination, etc., in addition to the phage display cloning and screening of Examples 1-4. *See, e.g.,* Specification at 12, lines 13-24. Because the starting enzymes described in the application were well known and readily available to a skilled artisan at the time this application was filed, one of skill in the art would appreciate how to apply the selection criteria to make a chimeric enzyme comprising a starting enzyme and a mimotope.

Two references previously discussed in relation to the novelty of this invention, *Brennan et al.* and *Benito et al.* (*See*, Answer at 4), establish that a skilled artisan would expect success in adding a heterologous binding sequence to a starting enzyme. These references describe chimeric enzymes comprising epitopes (rather than the mimotopes of the claimed assay methods). Benito et al., for example, describe five modified β-galactosidase enzymes that comprise an inserted epitope binding site, and show that antibody binding to two of the five modified enzymes modulates the enzymatic activity of the β-galactosidase enzyme. Brennan et al. describe three modified alkaline phosphatase enzymes that comprise an inserted epitope, and show

that all retain enzymatic activity and that one modified enzyme's activity is modulated upon antibody binding. This level of experimentation is hardly "undue." *See*, *Hybritech*, 802 F.2d at 1384, 231 USPQ at 94; *see also*, *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1998) (finding claims enabled when at least one antibody that fell within the scope of the claims was produced by a procedure, repeated three times).

Thus, guided by the specification, one skilled in the art would analyze the known structure and function of a selected starting enzyme, identify a site for insertion of a mimotope based on the detailed criteria of the specification, and using routine cloning techniques and screening assays, make chimeric enzymes having the desired properties for use in the claimed methods. *Brennan* explains that one skilled in the art expects this selection approach to work, stating that this approach is "likely" to create a modified enzyme that "not only preserve[s] high catalytic activity but also allows for inhibition of enzyme activity upon antibody binding." *Brennan* at 509. Also, as Appellants argued before, there can be no credible dispute that no undue experimentation is required for one skilled in the art to substitute a mimotope for the epitopes of *Benito* and *Brennan*. Opening Brief at 16, lines 9-12. Given the disclosed methods of making libraries of modified enzymes, and the disclosed methods of screening recombinant libraries to identify chimeras, the specification enables one skilled in the art to make chimeric enzymes useful in the claimed methods beginning with essentially any starting enzyme. *See*, *PPG Industries, Inc. v. Guardian Industries, Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) ("[A] considerable

amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance").

The Examiner's assertion that starting enzymes have distinct properties is not sufficient to out weigh this objective evidence of the knowledge and level of skill in the art. The Examiner further asserts that the skilled artisan would require 1) the primary amino acid or nucleic acid sequence for non-β-lactamase chimeric enzymes, 2) identification of the catalytic and binding sites for each, 3) guidance to where the sequence inserts of the mimotope can be made, and 4) the effect of such modifications on the functionality of different enzyme constructs to avoid undue experimentation.

Appellants disagree. The information of items 1 and 2 is well-known, well characterized, and readily available to one of ordinary skill in the art, based on the description of starting enzymes in the specification. As to item 3, the specification provides selection guidelines for where the sequence inserts of the mimotope can be made, and as shown in *Brennan* and *Benito* such selection was well within the level of skill in the art. And finally, the specification provides simple methods to screen for the functionality of different constructs, given the knowledge of a skilled artisan, which includes routine assays for the activities of appropriate starting enzymes.

The disclosure of this application, coupled with information known in the art, thus teaches how to practice the claimed methods with any chimeric enzyme without undue experimentation.

III. Methods Using Chimeric Enzymes Are Described by the Specification As-Filed

The Examiner rejects claims 13-23 and 25-29 for allegedly failing to satisfy the written description requirement, stating that the specification does not convey that Appellants were in possession of the claimed methods for using the full scope of the chimeric enzymes of the claims at the time the application was filed. The Examiner maintains that the specification does not describe a representative number of chimeric enzymes, and that because there is substantial variation in the genus of chimeric enzymes, written description of each member of the genus will be necessary. Answer at 18, line 22 to 19, line 1. As discussed above, the Examiner mischaracterizes the claims, confusing the issues on appeal. *See, e.g.*, Answer at 17 and 24; *Cf.* Answer at 5.

To satisfy the written description requirement, an application must describe the claimed invention so that one skilled in the art can recognize what is claimed. *Enzo Biochem., Inc. v. GenProbe, Inc.*, 323 F.3d 956, 968, 63 USPQ2d 1609, 1616 (Fed. Cir. 2002). As for enablement, the focus of the inquiry for satisfying the written description requirement is whether the *claimed* subject matter is adequately described. *See, e.g., Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 27 USP 177, 179 (Fed. Cir. 1985). It is well established that the claimed subject matter "need not be described in haec verba" in the specification in order to satisfy the written description requirement. *In re Smith*, 481 F.2d 910, 914, 178 USPQ 620, 624 (CCPA 1973).

The Federal Circuit has recently clarified that to describe a method of use of a compound, "the inventor cannot lay claim to that subject matter unless he can provide a

description of the compound sufficient to distinguish infringing compounds." *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926, 69 USPQ2d 1886, 1894 (Fed. Cir. 2004). The Examiner relies on this case in rejecting the method claims for alleged failure to describe the full scope of the chimeric enzymes that might possibly be used as labels in the claimed assay methods. Answer at 20-21. The result of the *Rochester* case, however, does not support an inference that the instant claims are inadequately described. In *Rochester*, the claims to methods of use of a novel group of compounds were rejected when the application included *no* exemplary compounds, and indeed the inventors had neither possession nor knowledge of any compound within the scope of the limitation at issue. Further, the inventors in *Rochester* disclosed no method for making any compound that could be used to practice the claimed method, or even any evidence that any such a compound was known at the time the application was filed. It is well established that molecules are not adequately described in an application by setting forth their function alone. *See*, *Regents of the Univ. of Calif. v. Eli Lilly & Co., Inc.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997).

Unlike the facts of *Rochester*, this application reduces chimeric β-lactamase enzymes to practice. The application also describes many other well-known enzymes with known structures, chemical formulas, and physical properties that could be used to make non-β-lactamase chimeric enzymes. As argued below, the description is more than sufficient to distinguish compounds the use of which would infringe the pending method claims and to establish to a skilled artisan reading the specification that the

inventors were in possession of the full scope of the claimed invention when the application was filed.

In the his Answer, the Examiner argues that the full scope of the chimeric enzymes is not described, alleging that "no description is provided in the specification for the insertion of β-lactamase specific mimotopes into any enzyme construct." Answer at 24. The Examiner appears to object that the position for insertion of a mimotope within a starting enzyme "would be impossible to determine" and that the specification does not clarify whether "the same mimotope sequences . . . [for] chimeric β-lactamase(s) [will] be effective as mimotopes [*sic*] insertions into any enzyme." Answer at 24.

First, Appellants note that the Examiner acknowledges that numerous embodiments of chimeric enzymes are reduced to practice in this application, but he states that "the mention in passing of possible target molecules on pages 5 and 6 of the instant specification, is not considered to sufficiently describe the claimed genus [of chimeric enzymes]." Answer at 24. As noted above, this reference to a "claimed genus" is inappropriate.[7] No chimeric enzymes are claimed.

In reaching his conclusion, the Examiner fails to consider the full scope of the relevant disclosure. In addition to the numerous chimeric enzymes comprising a β-lactamase starting enzyme that are reduced to practice in this application, many other

[7] Appellants respectfully note that the enzymes described on pages 5-6 of the specification are *starting* enzymes, not chimeric enzymes. The chimeric enzymes useful in the claimed methods comprise a starting enzyme and a mimotope. *See, e.g.*, Specification at 2-3 (explaining that "starting enzymes" are a "target molecule" in which an enzyme is the starting material).

chimeric enzymes are described by listing over 20 representative starting enzymes (a subset of "target molecules") and the properties that make them suitable for the instant invention. *See, e.g.*, Specification at 15, lines 12-18. Representative mimotopes for the chimeric enzymes, as well as specific sites for inserting mimotopes in a starting enzyme and guidance sufficient to define other specific sites are also described. *See* Specification at 10-11, for example.

Exemplary starting enzymes that are selected for a desirable detectable activity and that are directly amenable to the methods of the claims are provided as a list of well-known enzymes that have well-characterized activities. Specification at 5-6. In most cases, the enzyme names describe their enzymatic activity. Appellants note that β-lactamase is one example of this type of starting enzyme for which multiple chimeric species are fully described and characterized. The specification additionally identifies factors to consider when modifying a starting enzyme, such as to modulate the enzyme's catalytic activity with a mimotope placed near the catalytic site and thereby create a chimera in which the enzyme activity depends on the presence or absence of a binding molecule.

For these starting enzymes, the specification teaches that modifications should be made near, but not in, the active site of the enzyme. The specification also teaches that modifications should be made to regions that are not conserved between similar enzymes or to predicted secondary structural features such as sites predicted to be loops and sites susceptible to limited proteolysis in order to increase the likelihood that the activity of the chimeric enzyme will be maintained. Additionally, the specification

teaches that modifications predicted to be on the surface of the enzyme increase the likelihood that the mimotope is accessible to the binding molecule. *See, e.g.*, Opening Brief at 17-18 and Specification at 10-12 and 36-37.

The β-lactamase enzymes, from which chimeric enzymes were made according to these guidelines, exemplify this group of starting enzymes. The specification explains that the binding of a binding molecule to a chimeric enzyme comprising another starting enzyme can modulate the chimeric enzyme activity via a different mechanism. For modulation of the activity of a chimeric enzyme comprising a starting enzyme such as a serine protease, the specification describes, for example, insertion of a mimotope in the region of Arg 15-Ile 16 in chymotrypsinogen to prevent cleavage to chymotrypsin. To modulate the activity of a chimeric enzyme whose activity is, for example, regulated by its state of phosphorylation, the specification describes adding a mimotope to interfere with phosphorylation on Ser 14 of glycogen phosphorylase. Specification at 9, lines 5-22.

Further, the Examiner provides no reasoned basis to question the function of the wide variety of mimotopes in a different chimeric enzyme, when those mimotopes are disclosed and assessed as part of chimeric β-lactamase in Examples 3 and 4 of this application. The epitope chimeras known in the art, and described, for example, in *Brennan* (chimeric alkaline phosphatases) and in *Benito* (chimeric β-galactosidases) are evidence of success that counters the Examiner's asserted concern. These references also indicate that a skilled artisan would expect mimotopes to function in the various starting enzymes described in the specification as-filed.

In summary, the description provides a representative number of starting enzymes, mimotopes, and sites within the starting enzymes for insertion of a mimotope, as well as particular guidance on how to select other insertion sites. Unlike the facts of *Rochester*, this application involves use of well-known starting enzymes, with known functions, structures, and structure-function relationships. Further specific sites for inserting a mimotope in β-lactamase, chymotrypsinogen, and glycogen phosphorylase, for example, are described in the specification. The known characteristics of other starting enzymes make sites for positioning mimotopes in the same apparent to a skilled artisan. Appellants therefore respectfully submit that, even if the Examiner is correct that the specification must describe the full scope of chimeric enzymes that could be used in the claimed methods, one of skill in the art, reading the application as filed, would appreciate that the inventors possessed the full scope of the chimeric enzymes useful in the claimed methods, and that the written description rejection of the claims should be withdrawn.

IV. Conclusion

Appellants respectfully submit that the rejected claims satisfy the enablement and written description requirements of 35 U.S.C. § 112, paragraph 1. The Examiner's grounds for rejection have not established *prima facie* non-enablement or lack of written description of the claims, and even if the Board determines that the *prima facie* case for either rejection is established, Appellants present evidence to show that the claims are enabled and described.

If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: August 26,2005

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